1. rejected claims 1, 4, and 11-19 under 35 U.S.C. section 112, first paragraph.

2. rejected claims 1, 4, and 11-19 under 35 U.S.C. section 112, second paragraph.

III. Amendments to the Claims

Applicant hereby cancels claims 4 and 16-19 without prejudice to further prosecution at a later date.

The claim amendment "wherein the neuromuscular disorder or condition is selected from the group consisting of disorders of ocular motility; dystonia; tremors, tics, segmental myoclonus; spasms; spasticity; tension headaches; levator pelvic syndrome; spina bifida, tardive dyskinesia; Parkinson's, and; stuttering" is supported by at least page 5, lines 19-35 of the specification.

The claim amendment "intramuscular or subcutaneous administration" is supported by at least page 9, line 32 continuing to page 10, line 1 of the specification.

The claim amendment "up to 1,000 units of botulinum toxin type A" is supported by at least page 11, lines 10-11 of the specification.

The claim amendment that the loss of clinical response is determined by "a failure of the administered botulinum toxin type A to achieve a marked reduction of or to substantially alleviate a symptom of the neuromuscular disorder or condition" is supported by at least Example 1 on page 13 of the specification which states that the type A toxin causes the symptoms of the disorder to be "markedly reduced" and that when the symptoms are no longer markedly

reduced (i.e. "a loss of clinical response is noted"), the type B toxin is then administered until the symptoms are again "markedly reduced". This claim amendment is also supported by Example 2 on pages 14-15 of the specification which states that the first toxin causes the symptoms to be "substantially alleviated" and when this in no longer the case, the type B toxin is then administered and the symptoms are then again "substantially alleviated".

The claim amendment of "at least about 80 units of a botulinum toxin type B" is supported by at least line 13 of page 11 of the specification.

IV. The Section 112(1) Rejection

The Office Action rejected claims 1, 4, and 11-19 under 35 U.S.C. §112, first paragraph for lack of enablement on the bases that:

1. "...although it is true that botulinum toxin has been shown to be useful in treatment of different disorders associated with dysfunction of muscle innervation, the instant specification is not found to be enabling...for any 'neuromuscular disorder... "(page 3 of the Office Action).

2. "It is not clear and it is not explained how to approximate the proper time when the patient experiences loss of clinical response to botulinum toxin type A.." (page 4 of the Office Action).

3. "It is also not apparent what is the therapeutically effective amount..." (page 4 of the Office Action).

4. The instant specification does not provide any support for the estimation of development of neutralizing antibodies." (page 4 of the Office Action).

Applicants believe that the section 112(1) rejection has been overcome by the amended claims. Thus (using the same 1-4 numbering system as above):

1. The claims have been amended to the specific disorders of muscle innervation set forth in the specification. Thus, the objection in the Office Action that the instant specification is not enabling for any neuromuscular disorder has been overcome because all claims are now limited to the specific neuromuscular disorders set forth at page 5, lines 19-35 of the specification. Hence this basis for the section 112(1) objection has been overcome.

2. The claims have been amended to clearly show that the time when the patient experiences a loss of clinical response to botulinum toxin type A is the time when there is "a failure of the administered botulinum toxin type A to achieve a marked reduction or to substantially alleviate a symptom of the neuromuscular disorder or condition" being treated (all claims). Hence this basis for the section 112(1) objection have been overcome.

3. "therapeutically effective amount" has been amended in all claims to up to 1000 units of type A toxin and at least 80 units of type B toxin. Hence this basis for the section 112(1) objection have been overcome.

4. All claims directed to the development of neutralizing antibodies have been cancelled. Hence this basis for the section 112(1) objection have been overcome.

To further clarify the claims, the amended claims specify administration by intramuscular or subcutaneous administration.

For these reasons the section 112(1) rejection should be withdrawn.

V. The Section 112(2) Rejection

The Office Action rejected claims 1, 4, and 11-19 under 35 U.S.C. §112, second paragraph on the basis that "therapeutically effective amount" is not clear.

All claims have been amended to limit the claims to administration of up to 1000 units of type A toxin followed by at least 80 units of type B toxin. Hence the rejection has been overcome and should be withdrawn. It is well within the ability of a person of ordinary skill in the field of the present invention (i.e. a doctor treating a disorder of muscle innervation) to choose an amount of a botulinum toxin type A to treat the claimed disorders. For example it is well known that 1-3 units of type A toxin are used to treat a disorder of ocular mobility, whereas 200 units of type A toxin can be used to treat the much larger spasmodic thigh muscle (see e.g. Gracies J-M, et al., *Botulinum Toxin Therapy*, Neurologist 2000;6(2):98-115 (copy attached) which sets forth the known dosing amounts of type A toxin to use to treat various muscle innervation disorders . Additionally, as a rule of thumb physicians typically use an amount of type B toxin which is 50 times the amount of the type A toxin used to treat the same disorder. See e.g. Carruthers, A., et al *Toxins 99, New Information about the Botulinum Neurotoxins*, Dermatol Surg 2000;26(3):174-176. Note in particular page 176 left hand side of this publication where "Neurobloc" is the trade name for the type B toxin and "Botox" is the trade name for the type A toxin . Finally, please note the publication Brin M.F., et al, *Safety and efficacy of Neurobloc (botulinum toxin type B) in type A-resistant cervical dystonia*, Neurology 53;Oct 1999:2(2), 1431-1438, which discloses use of type A toxin to treat a disorder of muscle innervation until a lack of clinical response develops followed by use of the type B toxin in the same patient to treat the same condition.

For these reasons the section 112(2) rejection should be withdrawn.

VI. Conclusion

All issues raised by the Office Action have been addressed. Examination and allowance of claims 1 and 11-15 is requested.

Respectfully Submitted,

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UNMARKED VERSION OF THE CLAIMS

1. A method of treating a patient suffering from a neuromuscular disorder or condition wherein the neuromuscular disorder or condition is selected from the group consisting of: disorders of ocular motility; dystonias; tremors; tics; segmental myoclonus; spasms; spasticity; tension headache; levator pelvic syndrome; spina bifida, tardive dyskinesia; Parkinson's disease and; stuttering, the method comprising intramuscular or subcutaneous administration to the patient of up to 1,000 units of a botulinum toxin type A until the patient experiences loss of clinical response to the administered botulinum toxin type A, as determined by a failure of the administered botulinum toxin type A to achieve a marked reduction of or to substantially alleviate a symptom of the neuromuscular disorder or condition, and thereafter administering to the patient at least about 80 units of a botulinum toxin type B to thereby again achieve a marked reduction or a substantial alleviation of a symptom of the neuromuscular disorder or condition being treated.

11. The method of claim 1, wherein the neuromuscular disorder or condition is cervical dystonia.

12. A method of treating dystonia in a patient, the method comprising intramuscular or subcutaneous administration to a patient with dystonia of up to 1,000 units of a botulinum toxin type A until the patient experiences loss of clinical response to the administered botulinum toxin type A, as determined by a failure of the administered botulinum toxin type A to achieve a marked reduction of a symptom of the dystonia, and thereafter administering to the patient at least about 80 units of a botulinum toxin type B.

13. The method of claim 12, wherein the dystonia is cervical dystonia.

14. The method of claim 13, wherein treating the cervical dystonia reduces the severity of an abnormal head position symptom of the cervical dystonia.

15. The method of claim 13, wherein treating the cervical dystonia reduces a neck pain associated with the cervical dystonia.